Medical Coverage Policy

Effective Date **04/15/2023**
Next Review Date **04/15/2024**
Coverage Policy Number **0355**

Liver and Liver-Kidney Transplantation

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Overview

This Coverage Policy addresses liver transplantation and simultaneous liver-kidney (SLK) transplantation.

Coverage Policy

Liver transplantation is considered medically necessary for an individual with ANY of the following indications:

- end-stage liver failure
- hepatocellular carcinoma and BOTH of the following criteria are met:
  - stage T2 lesion (single lesion ≤ 5 cm OR up to three separate lesions, none larger than 3 cm)
  - alpha-fetoprotein (AFP) level ≤ 1000 ng/mL
- hepatoblastoma which is confined to the liver
- metabolic disease with intact hepatic synthetic function (e.g., type I hyperoxaluria, familial homozygous hypercholesterolemia, familial amyloidosis)
- unresectable perihilar or hilar cholangiocarcinoma with ALL of the following:
  - measures ≤3cm in radial diameter

  - absence of intrahepatic or extrahepatic metastasis,
  - without nodal disease
- neuroendocrine/gastroenteropancreatic (GEP) tumors with ALL of the following:
  - unresectable liver metastasis
  - prior complete resection of the primary GEP
  - absence of extrahepatic metastasis
  - failure to respond to medical and/or interventional treatment
  - severe hypoglycemia, poorly controlled hyperglycemia, cardiac distress, respiratory distress or other symptoms directly attributable to aberrant GEP tumor production of life-threatening hormones such as insulin, catecholamines, or histamine

Liver retransplantation is considered medically necessary for an individual considered to have a significant chance of success and who still meet eligibility criteria for primary transplantation for ANY of the following indications:

- primary graft failure
- hepatic artery thrombosis
- severe rejection
- recurrence of the disease which prompted the initial liver transplantation

Simultaneous liver-kidney (SLK) transplantation is considered medically necessary for an individual 18 years or older who meets medical necessity criteria for liver transplantation with ANY of the following indications:

- chronic kidney disease (CKD) with a measured or calculated glomerular filtration rate (GFR) ≤ 60 mL/min for more than 90 consecutive days and ANY of the following:
  - receiving regularly administered dialysis as an end-stage renal disease (ESRD) patient in a hospital based, independent non-hospital based, or home setting
  - at the time of registration on the kidney waiting list, the individual's most recent measured or calculated creatinine clearance (CrCl) or GFR is ≤ 30 mL/min
  - on a date after registration on the kidney waiting list, the individual's measured or calculated CrCl or GFR is ≤ 30 mL/min
- sustained acute kidney injury and at least ONE of the following for the previous 6 weeks:
  - receiving dialysis at least once every 7 days
  - individual has a measured or calculated CrCl or GFR that is consistently ≤ 25 mL/min
- a diagnosis of ANY of the following:
  - hyperoxaluria
  - atypical hemolytic uremic syndrome (HUS) from mutations in factor H or factor I
  - familial non-neuropathic systemic amyloidosis
  - methylmalonic aciduria

Liver transplantation is considered not medically necessary for an individual with ANY of the following contraindications to transplant surgery:

- ongoing alcohol abuse
- active extrahepatic malignancy that is expected to significantly limit future survival
- colorectal cancer metastatic to the liver
- known intrahepatic or central cholangiocarcinoma
- persistent, recurrent or unsuccessfully treated major or systemic infections
- systemic illness or comorbidities that would be expected to substantially negatively impact the successful completion and/or outcome of transplant surgery
- a pattern of demonstrated noncompliance which would place a transplanted organ at serious risk of failure
- human immunodeficiency virus (HIV) disease unless ALL of the following are noted:
  - cluster determinant (CD)4 count >100 cells/mm^3

- HIV-1 ribonucleic acid (RNA) undetectable
- stable antiretroviral therapy for more than three months
- absence of serious complications associated with HIV disease (e.g., opportunistic infection, including aspergillus, tuberculosis, coccidioidomycosis; or resistant fungal infections; or Kaposi's sarcoma or other neoplasm)

- donor with:
  - ongoing alcohol abuse
  - active malignancy, with the exception of non-melanotic skin cancer
  - persistent, recurrent or unsuccessfully treated infections, including hepatitis A, B or C or HIV
  - active systemic illness or serious comorbidities that would be expected to substantially negatively impact the successful completion and/or outcome of transplant surgery
  - active systemic illness that is likely to negatively affect survival

Mechanical perfusion systems for use with liver transplantation are considered experimental, investigational or unproven for ANY indication.

General Background

Liver transplantation (LT) is a complex operation requiring vascular reconstruction of the hepatic artery, the portal vein, and the hepatic venous system. Surgical techniques, which continue to evolve, include the orthotopic approach, involving replacement of the recipient liver with the donor liver, and the heterotopic approach in which the recipient liver is left in place and the donor liver is transplanted to an ectopic site. The whole liver, a reduced liver, or a liver segment may be transplanted depending on whether the donor is cadaveric (deceased) or living.

Living-donor liver transplantation was introduced as an alternative to deceased donor transplantation in response to the shortage of available cadaveric donor organs and is used for both adults and children. The graft from a living donor is more commonly from a relative of the recipient. The success of this type of transplantation is based on the ability of the liver to regenerate in both the donor and the recipient. The graft must be of adequate size in order to function in the recipient. The risks and benefits of using a living-donor graft must be considered as there are surgical risks to both the recipient and the donor. Benefits to the recipient include a reduced chance of mortality related to waiting for a cadaveric-donor organ, a reduced likelihood of primary non-function of the graft, and a potential decrease in the chance of graft rejection and the need for immunosuppression. Ethical concerns regarding living donor liver transplantation (LDLT) are related to the potential for donor morbidity and mortality. Opponents argue that it is unacceptable to place a healthy donor at risk of long-term debility or death. Donation of the left lateral segment or left lobe, used primarily in pediatric transplantation, is associated with a 5 to 10 percent chance of surgical complications and a mortality rate of less than 1 percent. The estimated mortality for right lobe donation, used in adult-to-adult LDLT, is around 0.5 percent.

In 2020, 8906 adult liver transplants were performed in the United States. Living donation activity decreased after several years of growth. Adults represented 94.4% of liver transplant recipients, with 7979 deceased donor and 425 living donor liver transplants. The proportion of patients 65 years or older continued to grow, making up 22.4%. Among liver transplant recipients, 63.2% were male; 70.0% were White, 16.8% were Hispanic, 7.3% were Black, and 4.3% were Asian. In 2020, 502 pediatric liver transplants were performed in the United States, the lowest number in the past decade and a decrease of 8.9% from 2019. Multiorgan transplants accounted for 10.1%, most of which were simultaneous liver-kidney transplants (9.1%) (Scientific Registry of Transplant Recipients [SRTR]).

Mansour et al. (2022) performed an analysis of discharge data from the National Inpatient Sample (NIS), the largest publicly available inpatient care database in the United States, between 2016 and 2019. A total of 24,595 liver transplants were performed over the study period. Patients with a chronic liver disease hospital diagnosis were compared to the number of those who underwent a liver transplant (chronic liver disease includes cirrhosis, regardless of the etiology, and hepatocellular carcinoma). The author's multivariate analysis reveals that there remain many independent variables that are associated with inequalities in receipt of liver transplants.

- Females compared to males were less likely to receive liver transplantation.

- There were marked differences in liver transplantation rates based on patient race. Compared to White patients, Black and Native American patients were less likely to receive liver transplants while Asians and Hispanic patients were more likely to.
- The increase in income quartile was associated with an incremental increase in transplant rates. Additionally, patients with private insurance had much higher transplant rates compared to those with Medicare while patients without insurance had the lowest rates of transplantation.

Mathur et al. (2014) created an empirical measure of relative waiting list access termed the 'liver wait-listing ratio' (LWR). This metric captures the rate of wait-listing for a given group relative to those potentially eligible for transplant, namely, those who died from liver disease and those who were listed, less those already transplanted. Mathur calculated LWRs from national liver transplant registration data and liver mortality data from the Scientific Registry of Transplant Recipients and the National Center for Healthcare Statistics from 1999 to 2006. (Note: Model for End-stage Liver Disease [MELD] was adopted by UNOS in 2002.)
Results demonstrated that for both acute and chronic liver disease, Blacks had significantly lower LWRs compared with whites in each (pre-MELD and MELD) era, by at least 25%. This may be related to several factors, including differential rates of referral to liver transplant programs, racial/ethnic differences in disease progression, delays in diagnosis, differences in the quality of hospitals and outpatient care offered to Black patients, patient preferences, mistrust of transplant providers, socioeconomic differences, or even provider bias. However, once Black patients are listed, recent data suggest that they have similar liver transplant rates as white candidates (Mathur et al. 2014).

A literature review found that racial and ethnic minorities (Black and Hispanic patients) have lower rates of liver transplant (LT) referral, more advanced liver disease and hepatocellular carcinoma at diagnosis, and are less likely to undergo living donor LT (LDLT).

- Medicaid insurance has been associated with higher rates of chronic liver disease and poor waitlist outcomes.
- After LT, some studies found lower overall survival among Black compared with white recipients. Studies have also shown lower literacy and limited educational attainment were associated with increased post-transplant complications and lower use of digital technology. However, there are notable gaps in the literature on disparities in LT.

Detailed population-based estimates of the advanced liver disease burden and LT referral and evaluation practices, including for LDLT, are lacking (Nephew and Serper, 2021).

Indications for Liver Transplantation
The major indications for liver transplantation are irreversible hepatic failure or liver cancer**.** Each liver transplant candidate is assigned a score that reflects the probability of death within a 3-month period as determined by the Model for End-Stage Liver Disease (MELD) scoring system or the Pediatric End Stage Liver Disease (PELD) scoring system. Liver candidates can also be assigned a priority status if the candidate meets the requirements for that status. The Liver and Intestinal Organ Transplantation Committee establishes guidelines for review of status and MELD or PELD score exception requests. If a candidate's transplant program believes that a candidate's current MELD or PELD score does not appropriately reflect the candidate's medical urgency for transplant, the transplant program may submit a MELD or PELD score exception request to the National Liver Review Board (NLRB).

A liver distribution system based on acuity circles went into effect in February 2020. Since implementation of this policy change, waiting times have decreased for patients with a MELD score of ≥29, while waiting times have increased for those patients with a MELD score of ≤28. This has placed pressure on transplant programs to increasingly pursue DCD and other "marginal" livers for patients listed with a MELD score of ≤28. HCC patients no longer have a "ladder" model of increasing exception scores over time. This has significantly reduced access to standard criteria livers for patients with HCC. As a result, the utilization of DCD livers for patients with HCC has significantly increased (Croome, et al., 2023).

Contraindications to Liver Transplantation
Many factors affect the outcome of solid organ transplantation. Prior to transplantation a rigorous assessment of the recipient's medical status should be conducted to confirm that transplantation constitutes the best option for managing the patient's disease and that no contraindications exist. According to the American Association for

the Study of Liver Diseases (AASLD) and the American Society of Transplantation (Martin, et al., 2014), these are listed contraindications to liver transplant:

- MELD Score <15
- Severe cardiac or pulmonary disease
- AIDS
- Ongoing alcohol or illicit substance abuse
- Hepatocellular carcinoma with metastatic spread
- Uncontrolled sepsis
- Anatomic abnormality that precludes liver transplantation
- Intrahepatic Cholangiocarcinoma
- Extrahepatic malignancy
- Fulminant hepatic failure with sustained intracranial pressure >50 mm Hg or cerebral perfusion pressure <40 mm Hg*
- Hemangiosarcoma
- Persistent noncompliance
- Lack of adequate social support system

Colorectal liver metastases (CRLM)
In spite of the lack of UNOS/OPTN criteria for organ allocation specifically for CRLM, there are clinical trials being conducted that address the use of LT for colorectal liver metastases (CRLM). Preliminary studies report that some carefully selected patients may benefit from LT compared to current treatment options (Dueland, et al., 2020 [SECA II]; Smedman, et al., 2020 [SECA D arm]; Hagness, et al., 2013 [SECA I]). There is minimal prospective data and LT remains exploratory in the setting of CRLM. Additionally, several challenges remain including but not limited to defining appropriate selection criteria for these patients. Further evidence from ongoing and future well-designed trials are needed to determine if and to what extent there is a role for LT in liver-limited surgically unresectable colorectal liver metastases (Lebeck Lee, et al., 2022).

Human Immunodeficiency Virus (HIV)
Historically, HIV positivity has been considered a contraindication to solid organ transplantation. Access to liver transplantation was limited due to questions regarding life expectancy, clinical efficacy, and complications post-liver transplantation caused by interactions between antiviral therapy and immunosuppressive medications, and the increased risk of opportunistic infections.

More recently liver transplantation has become an acceptable treatment option for selected individuals who are HIV-positive. While overall survival is generally lower for individuals with HIV-infection compared to HIV-negative persons, monoinfection (i.e. HIV infection only) does not seem to be a significant risk factor for survival after liver transplantation. Orthotopic liver transplantation appears to be a safe therapeutic option in the short term for selected persons with HIV infection who have end-stage liver disease.

At present, AASLD criteria for liver transplantation include a CD 4 count >100/μL with a viral load anticipated to be completely suppressed at time of transplant (Martin, et al., 2014).

Donor Health
The health of the donor is also an important factor in liver transplantation outcomes. Hepatitis C virus (HCV) infection in the donor can affect the health of the donor liver, making individuals with persistent, recurrent, or untreated HCV infection unacceptable donors. Likewise, donor candidates who are hepatitis B surface antigen-(HbsAg) positive are also generally excluded from living-donor liver transplant donation to prevent transmission of disease to recipients. Factors which may negatively affect recipient outcomes after liver transplantation including ongoing alcohol abuse, active systemic illness, and malignancy, are also considered contraindications to donation.

Retransplantation of the Liver
Retransplantation may be appropriate for carefully selected patients experiencing graft loss if an improvement in survival is expected; however, liver retransplantation should be used with discretion in the emergency setting

and avoided in patients with little chance of success. In adults, the most common condition resulting in the need for retransplantation of the liver is recurrent infection with hepatitis C virus (HCV). Retransplantation in patients with HCV is controversial due to concerns of aggressive disease recurrence post retransplantation, and decreased patient and graft survival. Several retrospective cohort studies have examined the outcomes of patients retransplanted for recurrent HCV demonstrating lower patient and graft survival in some studies.

Simultaneous Liver-Kidney (SLK) transplantation
Since the introduction of the model for end-stage disease (MELD) score in 2002, there has been an increased use of SLK transplantation. Of all adult liver transplants in the US in 2019, 787 (9.4%) were multi-organ, most of which were simultaneous liver-kidney (SLK) transplants (704, compared with 347 in 2009). The reasons for this increase are multifactorial. First, allocation using the MELD score prioritizes patients with renal dysfunction, as the score incorporates both serum creatinine (Scr) and utilization of pretransplant renal replacement therapy (RRT). Second, superior outcomes have been observed following SLK in recipients with advanced pretransplant renal dysfunction. Finally, there has been a steady increase in the incidence of nonalcoholic fatty liver disease, resulting in more patients on the LT waiting list with this diagnosis (Bari, et al., 2021; Pita, et al., 2019; Singal, et al., 2019; Miles, et al., 2018).

Goyes et al. (2020) evaluated post-graft survival outcomes following Simultaneous Liver-Kidney Transplant (SLKT) following adoption of updated criteria in 2017. The UNOS OPTN database was used to identify Caucasian, African American (AA), and Hispanic patients who underwent SLKT from August 10 2017 to December 31 2019. Children (age < 18 years), patients listed as status 1, and living donor transplants were excluded.

- Hispanics presented more severe disease and had a higher MELD score at transplant than Caucasian and AA patients.
- Patients with non-alcoholic steatohepatitis (NASH) and alcohol-related liver disease (ALD) formed a larger proportion of the subjects undergoing SLKT in both Caucasians and Hispanics, while hepatitis C virus (HCV) was the most common disease present in AAs.
- There was no difference between racial/ethnic groups in post-transplant graft survival at six months, one year, and two years ($p = 0.905$).
- On multivariate Cox regression analysis, being male, cold ischemia, alcohol-related liver disease (ALD), and hepatitis C virus (HCV) were associated with a higher risk of graft failure.

Jay et al. (2020) retrospectively analyzed UNOS data for adult liver transplant recipients between January 1, 2002 and December 31, 2018. The aim was to compare survival following simultaneous liver-kidney transplantation (SLK), early kidney after liver transplantation (KALT), and liver transplantation alone (LTA) in adult patients. Early KALT was defined as 60 to 365 days between liver and subsequent kidney transplantation (reflecting safety net listing criteria). There were 6,774 SLK, 120 KALT at 60 to 365 days, and 11,501 LTA. Early KALT had equivalent survival compared with SLK, both for all KALT (hazard ratio [HR] 0.58, p=0.05) and for deceased donor (DD) KALT only (HR 0.72, p=0.32). Simultaneous liver-kidney transplantation was associated with improved survival compared with LTA (HR 0.82, $p < 0.01$). Early KALT was associated with a greater reduction in mortality compared with LTA, but this was not significant (HR 0.58, p=0.05). The authors concluded that early KALT has equivalent survival compared with SLK transplantation, both for all KALT and for DD KALT only, supporting the promise of the “safety net.”

Professional Societies/Organizations

American Association for the Study of Liver Disease (AASLD)/ American Society of Transplantation (AST): The AASLD and AST have published numerous joint guidelines, including some specific to liver transplantation.
Evaluation for Liver Transplantation in Adults: 2013 Practice Guideline by the AASLD and the American Society of Transplantation (Marin, et al., 2014) states liver transplantation (LT) is indicated for severe acute or advanced chronic liver disease when the limits of medical therapy have been reached. Recognition of cirrhosis per se does not imply a need for LT. Many patients with cirrhosis in the absence of an index complication such as ascites or variceal hemorrhage will not develop hepatic decompensation, although patients with cirrhosis have diminished survival compared to the population as a whole. Acute liver failure complications of cirrhosis include ascites,

chronic gastrointestinal blood loss due to portal hypertensive gastropathy, encephalopathy, liver cancer, refractory variceal hemorrhage and synthetic dysfunction.

Evaluation of the Pediatric Patient for Liver Transplantation: 2014 Practice Guideline by the American Association for the Study of Liver Diseases, American Society of Transplantation and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (Squires, et al., 2014) indications for LT include biliary atresia (32%), metabolic/genetic conditions (22%), acute liver failure (11%), cirrhosis (9%), liver tumor (9%), immune-mediated liver and biliary injury (4%), and other miscellaneous conditions (13%). Within these broad categories rest many rare conditions with myriad presentations.

American Society of Transplantation (AST): The AST has several Key Position Statements, including but not limited to Deceased Organ Donation, Insurance Coverage for Living Donors, and Insurance Coverage for Transplant Recipients, and Living Organ Donation. They also publish guidelines, including Long-Term Medical Management of the Pediatric Patient after Liver Transplantation, Long-Term Management of the Successful Adult Liver Transplant, Curricular Guidelines for Training in Transplant Hepatology, and a Position paper on Indications for pediatric intestinal transplantation.

National Comprehensive Cancer Network Guidelines™ (NCCN Guidelines™): The NCCN Guidelines (V.5.2022 — January 13, 2023) for Hepatobiliary Cancers address transplantation addresses liver transplantation as follows:

Principles of Surgery for HCC
Patients meeting the UNOS criteria (AFP level ≤1000 ng/ml and single lesion ≥2 cm and ≤5cm, or 2 or 3 lesions ≥1 cm and ≤3cm) should be considered for transplantation (cadaveric or living donation). There are patients whose tumor characteristics are marginally outside of the UNOS guidelines who should be considered for transplant. Furthermore, there are patients who are downstaged to within criteria that can also be considered for transplantation. Candidates are eligible for a standardized MELD exception if, before completing loco regional therapy, they have lesions that meet one of the following criteria:

- One lesions > 5cm and ≤ 8 cm
- Two or three lesions that meet all of the following: each lesion ≤ 5 cm with at least one lesion > 3cm and a total diameter of all lesions ≤ 8 cm
- Four or five lesions each < 3 cm and a total diameter of all lesions ≤ 8 cm

Patients with Child-Pugh Class A function, who fit UNOS criteria and are resectable, could be considered for resection or transplant. There is controversy over which initial strategy is preferable to treat such patients (NCCN, page HCC-D).

Extrahepatic cholangiocarcinoma /Presentation and Workup /Primary Treatment
Unresectable perihilar or hilar cholangiocarcinoma that measures ≤3cm in radial diameter, with the absence of intrahepatic or extrahepatic metastasis, and without nodal disease, as well as those with primary sclerosing cholangitis may be considered for liver transplantation at a transplant center that has an UNOS-approved protocol for transplantation of cholangiocarcinoma (NCCN, page EXTRA-1).

The NCCN Guidelines (V.3.2022 — January 25, 2023) for Colon Cancer does not address liver transplant. ‘When hepatic metastatic disease is not optimally resectable based on insufficient remnant liver volume, approaches using preoperative portal vein embolization, staged liver resection, or yttrium-90 radioembolization can be considered.’ (COL-C)

Organ Procurement & Transplantation Network (OPTN): The OPTN Policies document (OPTN, 2/01/2023) addresses Allocation of Livers and Liver-Intestines in Policy 9. Sections within the Policy address many topics related to liver transplant including Requirements for Hepatocellular Carcinoma (HCC) MELD or PELD Score Exceptions.

> OPTN Policy 9.5.I.ii Eligible Candidates Definition of T2 Lesions
> Candidates with T2 HCC lesions are eligible for a standardized MELD or PELD exception if they have an alpha-fetoprotein (AFP) level less than or equal to 1000 ng/mL and either of the following:

- One lesion greater than or equal to 2 cm and less than or equal to 5 cm in size.
- Two or three lesions each greater than or equal to 1 cm and less than or equal to 3 cm in size.

A candidate who has previously had an AFP level greater than 1000 ng/mL at any time must qualify for a standardized MELD or PELD exception according to Policy 9.5.I.iv: Candidates with Alpha-fetoprotein (AFP) Levels Greater than 1000.

OPTN Policy 9.5.I.iii Lesions Eligible for Downstaging Protocols
Candidates are eligible for a standardized MELD or PELD exception if, before completing local-regional therapy, they have lesions that meet *one* of the following criteria:

- One lesion greater than 5 cm and less than or equal to 8 cm
- Two or three lesions that meet all of the following:
  - at least one lesion greater than 3 cm
  - each lesion less than or equal to 5 cm, and
  - a total diameter of all lesions less than or equal to 8 cm
- Four or five lesions each less than 3 cm, and a total diameter of all lesions less than or equal to 8 cm

For candidates who meet the downstaging criteria above and then complete local-regional therapy, their residual lesions must subsequently meet the requirements for T2 lesions according to Policy 9.5.I.ii: Eligible Candidates Definition of T2 Lesions to be eligible for a standardized MELD or PELD exception. Downstaging to meet eligibility requirements for T2 lesions must be demonstrated by CT or MRI performed after local-regional therapy. Candidates with lesions that do not initially meet the downstaging protocol inclusion criteria who are later downstaged and then meet eligibility for T2 lesions are not automatically eligible for a standardized MELD or PELD exception and must be referred to the NLRB for consideration of a MELD or PELD exception.

OPTN Policy 9.5.I.iv Candidates with Alpha-fetoprotein (AFP) Levels Greater than 1000
Candidates with lesions meeting T2 criteria according to Policy 9.5.I.ii Eligible Candidates Definition of T2 Lesions but with an alpha-fetoprotein (AFP) level greater than 1000 ng/mL may be treated with local-regional therapy. If the candidate's AFP level falls below 500 ng/mL after treatment, the candidate is eligible for a standardized MELD or PELD exception as long as the candidate's AFP level remains below 500 ng/mL. Candidates with an AFP level greater than or equal to 500 ng/mL following local-regional therapy at any time must be referred to the NLRB for consideration of a MELD or PELD exception.

OPTN Table 9-17: Medical Eligibility Criteria for Liver-Kidney Allocation (2/01/2023) OPTN Policy)

If the candidate's transplant nephrologist confirms a diagnosis of:	Then the transplant program must report to the OPTN and document in the candidate's medical record:
Chronic kidney disease (CKD) with a measured or calculated glomerular filtration rate (GFR) less than or equal to 60 mL/min for greater than 90 consecutive days	At least *one* of the following: • That the candidate has begun regularly administered dialysis as an end-stage renal disease (ESRD) patient in a hospital based, independent non-hospital based, or home setting. • At the time of registration on the kidney waiting list, that the candidate's most recent measured or calculated creatinine clearance (CrCl) or GFR is less than or equal to 30 mL/min. • On a date after registration on the kidney waiting list, that the candidate's measured or calculated CrCl or GFR is less than or equal to 30 mL/min.
Sustained acute kidney injury	At least *one* of the following, or a combination of *both* of the following, for the last 6 weeks:

If the candidate's transplant nephrologist confirms a diagnosis of:	Then the transplant program must report to the OPTN and document in the candidate's medical record:
	• That the candidate has been on dialysis at least once every 7 days. • That the candidate has a measured or calculated CrCl or GFR less than or equal to 25 mL/min at least once every 7 days. If the candidate's eligibility is not confirmed at least once every seven days for the last 6 weeks, the candidate is not eligible to receive a liver and a kidney from the same donor.
Metabolic disease	A diagnosis of at least *one* of the following: • Hyperoxaluria • Atypical hemolytic uremic syndrome (HUS) from mutations in factor H or factor I • Familial non-neuropathic systemic amyloidosis • Methylmalonic aciduria

Kidney Disease: Improving Global Outcomes (KDIGO): The KDIGO 2020 Clinical Practice Guideline on the Evaluation and Management of Candidates for Kidney Transplantation guideline included recommendations regarding liver-kidney transplantation:

- Hyperoxaluria (oxalosis), primary and secondary 9.16.1: We suggest that candidates with primary hyperoxaluria type 1 be considered for combined or sequential liver-kidney transplantation (2C).
- Hepatitis C virus (HCV) 10.5.2.4.2: We recommend referring patients with HCV and decompensated cirrhosis for combined liver-kidney transplantation (1B) and deferring HCV treatment until after transplantation (1D).
- Liver disease 16.7.3: We recommend that candidates with cirrhosis or suspected cirrhosis be referred to a specialist with expertise in combined liver-kidney transplantation for evaluation (1B).

Description for grading recommendations:
Level 1: "We recommend". Most patients should receive the recommended course of action.
Level 2: "We suggest". Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.
A: High Quality of Evidence. We are confident that the true effect lies close to that of the estimate of the effect.
B: Moderate Quality of Evidence. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
C: Low Quality of Evidence. The true effect may be substantially different from the estimate of the effect.
D: Very low Quality of Evidence. The estimate of effect is very uncertain, and often will be far from the truth (Chadban, et al., 2020).

International Hepato-Pancreato-Biliary Association: The International Hepato-Pancreato-Biliary Association published Consensus Guidelines on Liver transplantation for non-resectable colorectal liver metastases (Bonney, et al., 2021). The purpose was to standardize nomenclature and define management principles in five key domains: patient selection, evaluation of biological behavior, graft selection, recipient considerations, and outcomes. The final consensus document includes 44 statements, standardized nomenclature, and a practical management algorithm

International Liver Transplantation Society (ILTS): The Working Group Report From the ILTS Transplant Oncology Consensus Conference (Hibi, et al., 2020) titled 'Liver Transplantation for Colorectal and Neuroendocrine Liver Metastases and Hepatoblastoma' published these Recommendations regarding CRLM:

1. LT can be a viable option in highly selected patients with unresectable CRLM with only liver involvement (moderate level of evidence and moderate recommendation).

2. LT for CRLM with low Oslo score ≤2 (maximum tumor diameter ≤ 5.5 cm, pretransplant carcinoembryonic antigen ≤80 µg/L, response to chemotherapy, time interval: diagnosis to LT ≥ 2 y) may improve the 5-year overall survival rates over those achieved with the current standard of care (moderate level of evidence and moderate recommendation).
3. Minimization of immunosuppression is recommended (low level of evidence and moderate recommendation).
4. Aggressive treatment of all posttransplant resectable recurrences is recommended (low level of evidence and moderate recommendation).
5. There is a need for an international registry to coordinate data collection and design further studies on LT for CRLM (moderate level of evidence and moderate recommendation).

The document also addressed neuroendocrine liver metastases and hepatoblastoma.

Mechanical Perfusion Systems

Mechanical perfusion (MP) of livers with blood or preservation solution is proposed as an alternative to static cold storage (SCS). The term machine or mechanical perfusion (MP) summarizes a variety of dynamic, continuous perfusion, and preservation techniques used with the goal to prevent decline of allograft quality following organ retrieval and ischemia-reperfusion injury. Researchers propose MP has the capacity to expand the donor pool and decrease the rate of organ discard. Today, variations of mechanical perfusion (MP) are studied in clinical trials:

- Normothermic machine perfusion (NMP) is the ex situ perfusion of livers with oxygenated blood and medications at body temperature to preserve the liver in a physiological, functioning state. Normothermic liver perfusion needs the full range of liver nutrients and physiologic oxygen availability to keep livers alive. Normothermic liver machine perfusion can be performed during or immediately after procurement at the donor site, requiring transport of a complex machine to the site of organ procurement. The alternative is an application of machine liver perfusion limited to the transplantation center with graft transport under the standard static cold storage. This strategy is known as “end-ischemic” perfusion. Normothermic regional perfusion (NRP) approach consists of cannulating donor iliac vessels and commencing perfusion of the abdominal compartment organs shortly after donor circulatory arrest. The donor is put on a perfusion device for 2 to 4 h with subsequent cold flush and standard procurement.

- (Dual) Hypothermic oxygenated machine perfusion (HOPE/D-HOPE) involves ex situ continuous perfusion of the liver with a cooled, oxygenized perfusate. ‘Dual’ refers to active oxygenation and perfusion via both the portal vein and the hepatic artery versus solely via the portal vein. Also called sub-normothermic (SNMP) and hypothermic machine perfusion (HMP). There is metabolic need for oxygen during hypothermic conditions, although at a low level. In contrast to normothermic perfusion, hypothermic oxygenated perfusion (HOPE) needs only a short time for metabolic conversion due to the decreased metabolic demand in the cold.

Mechanical Perfusion Systems - U.S. Food and Drug Administration (FDA)
Currently there are two ex situ mechanical perfusion devices that are FDA approved for clinical use.

The TransMedics® Organ Care System (OCS™) Liver received FDA PMA approval September 28, 2021 (P200031) (TransMedics, Inc., Andover, Massachusetts). The OCS Liver is a portable platform designed to maintain donor livers in a near-physiologic, normothermic, and perfused state. The OCS Liver is comprised of three major components: 1) OCS Liver Console; 2) OCS Liver Perfusion Module and Accessories (Perfusion Set [LvPS]); 3) OCS Liver Bile Salts Set.

- Indications for Use are stated as: “the TransMedics® Organ Care System (OCS™) Liver is a portable extracorporeal liver perfusion and monitoring system indicated for preservation and monitoring of hemodynamics and metabolic function which allows for ex-vivo assessment of liver allografts from donors after brain death (DBD) or liver allografts from donors after circulatory death (DCD) ≤55 years old and with ≤30 mins of warm ischemic time, macrosteatosis ≤15%, in a near-physiologic, normothermic and functioning state intended for a potential transplant recipient.”

The OrganOx metra® System received FDA PMA approval December 9, 2021 (P200035) (OrganOx, Limited; Oxford UK). The OrganOx metra is a fully automated normothermic machine perfusion (NMP) device for the preservation and transport of donor livers destined for transplantation. It is designed to transport and preserve donor livers prior to transplantation and includes three main components: 1) a reusable base unit that contains software, hardware, and a trolley or hardcover; 2) a sterilized, single use, disposable fluid management circuit; and 3) the solutions required for perfusion.

- Indications for Use are stated as: "the OrganOx metra® is a transportable device intended to be used to sustain donor livers destined for transplantation in a functioning state for a total preservation time of up to 12 hours. The OrganOx metra® device is suitable for liver grafts from donors after brain death (DBD), or liver grafts from donors after circulatory death (DCD) ≤40 years old, with ≤20 mins of functional warm ischemic time (time from donor systolic blood pressure <50 mmHg), and macrosteatosis ≤15%, in a near-physiologic, normothermic and functioning state intended for a potential transplant recipient.

The FDA approval was based on clinical trial NCT02775162, which has not yet been published in the peer-reviewed scientific literature.

Non-FDA approved systems
According to Bridge to Life, Ltd. website, Bridge to Life announced investigational device exemption (IDE) approval by the U.S. Food and Drug Administration (FDA) for its VitaSmart™ Liver Machine Perfusion System on December 14, 2021. The website states The VitaSmart™ Liver Machine Perfusion System "provides clinicians with the ability to implement hypothermic oxygenated perfusion (HOPE) of liver grafts in the transplant center operating room after ex-vivo cold storage prior to transplant surgery".

According to XVIVO's website, XVIVO (XVIVO Perfusion AB) was granted Breakthrough Device Designation from the FDA on September 20, 2022 for their Liver Assist device, "indicated for ex-vivo oxygenated machine perfusion for preservation of donor livers prior to transplantation". XVIVO Perfusion AB ("XVIVO") completed the acquisition of Organ Assist B.V. ("Organ Assist") in September 2020. The website says that Liver Assist is only device for ex vivo liver perfusion at temperatures ranging from hypothermic to normothermic.

The manufacturer site says Paragonix LIVERguard™ Donor Liver Preservation System "is FDA cleared". No mention of LIVERguard™ was located on the FDA website. The manufacturer site states these are the Indications for Use:

- The Paragonix LIVERguard™ Donor Liver Transport System is intended to be used for the static hypothermic preservation of liver during transportation and eventual transplantation into a recipient using cold storage solutions indicated for use with donor livers.
- The intended organ storage time for the LIVERguard™ system is up to 15 hours.
- Donor livers exceeding clinically accepted static hypothermic preservation times should be evaluated by the transplant surgeon to determine transplantability in accordance with accepted clinical guidelines and in the best medical interest of the intended recipient.
- Note: A partial liver can be transported via the LIVERguard™ System by packaging liver per institutional protocol and UNOS guidelines

Mechanical Perfusion Systems - Literature Review
There are unresolved issues surrounding organ preservation for transplantation. There is no uniform agreement on indications for the use of various machine perfusion devices. Inclusion/exclusion criteria in published studies vary by device, by donor status/donation criteria, and other factors. Numerous clinical trials are underway or recruiting on the Clinicaltrials.gov website. Long term health outcomes will help to identify the potential optimal cohort characteristics. Additionally, there is a lack of US federal government / OPTN guidance regarding the use of these devices (Croome, et al., 2023; Sousa Da Silva, et al., 2022; Mugaanyi, et al., 2022; van Beekum, et al., 2021).

A multicenter randomized controlled trial (RCT) (International Randomized Trial to Evaluate the Effectiveness of the Portable Organ Care System Liver for Preserving and Assessing Donor Livers for Transplantation) (PROTECT) was conducted. The OCS Liver device from TransMedics® was used.

- The trial was designed to overcome the limitations of ischemic cold storage (ICS), limiting the period of ischemia and providing physiologic assessment of liver graft function. The PROTECT trial prespecified

donor characteristics from donation after brainstem death (DBD) and donation after circulatory death (DCD) donors that are known to be more vulnerable to ICS associated damage. The PROTECT trial was designed to test for both noninferiority and superiority if noninferiority was met.

- The PROTECT trial objective was to compare the safety and the effectiveness of the OCS Liver vs ICS for Donors with at least 1 of the following characteristics: (1) 40 years of age or older; (2) expected total cross-clamp/cold ischemic time of 6 or more hours; (3) DCD donors if 55 years or younger; or (4) macrosteatotic livers (≤40%). Donor liver exclusion criteria included living donors, split livers, livers requiring accessory vessel reconstruction, or moderate to severe traumatic liver injury. Recipient exclusion criteria included younger than 18 years, acute or fulminant liver failure, prior solid organ or bone marrow transplant, chronic kidney failure, multiorgan transplant, ventilator dependence, or hemodynamic compromise.
- The primary effectiveness end point was the incidence of early allograft dysfunction (EAD) which was analyzed by calculating the sample proportion of patients meeting the primary effectiveness end point, as well as an exact (Clopper-Pearson) 95% CI for the corresponding population proportion.
- Per-protocol population consisted of 293 patients (151 in the OCS Liver group and 142 in the ICS group).
- The authors reported the primary effectiveness end point was met by a significant decrease in EAD (27 of 150 [18%] vs 44 of 141 [31%]; P = .01).
- Overall 12-month patient survival was 94.0% (142 of 151) for the OCS Liver group and 93.7% (133 of 142) for the ICS group (Markmann, et al., 2022).

A multicenter randomized controlled trial was conducted at ten European centers in six countries. The Liver Assist® (Organ Assist, now XVIVO) device was used.

- A total of 170 livers donated after brain death (DBD) were transplanted. Exclusion criteria included all partial or combined liver transplants, living donor or DCD liver transplantation, cold ischemia times of more than 15 hours, and an acute or unexpected medical contraindication for LT.
- Conventionally cold stored (control group, N=85) was compared to cold stored AND subsequently treated by 1-2h hypothermic oxygenated perfusion (HOPE) before implantation (HOPE group, N=85). The primary endpoint was the occurrence of at least one post-transplant complication per patient, graded by the Clavien score of ≥III, within 1- year after LT.
- All patients completed the 1 year follow up, with the exception of deaths during this time (n=8). A total of 1190 complications were documented for all study patients during 1 year after LT with no patient lost to follow-up. The proportion of patients with at least one complication ≥ Clavien IIIa did not significantly differ between groups with 54.1% (46/85) in the control group and 51.8% (44/85) in the HOPE Group (p=0.76).
- There was also no significant difference in all pre-specified secondary endpoints, which focus on lab values, initial ICU- and hospital stay, and survival. However, many patients developed more than one major complication within one year follow-up. The extent of post-transplant morbidity was only recognized by the frequency and the severity grade of complications, with a 74% lower number of liver related Clavien ≥IIIb complications in the HOPE-arm, compared to the control group.
- The authors noted there was no relevant clinical difference between the two groups in the severity of serious adverse events and that the post hoc findings of this trial should be further validated in future studies (Schlegel, et al., 2023).

A multicenter randomized controlled trial evaluated normothermic machine perfusion (NMP). In the static cold storage (SCS) arm, the organ retrieval, storage and the transplant were conducted according to standard practice. In the NMP arm, following removal from the donor, the liver was attached to the OrganOx metra NMP device.

- Inclusion criteria for donors and recipients were deliberately broad to represent the full spectrum of clinical practice. Whole livers from brainstem death donors (DBD) and declared dead by cardiovascular criteria (DCD) donors at least 16 years of age were eligible. Recipients were eligible provided they were at least 18 years old and listed for a liver-only transplant, excluding those with fulminant liver failure.
- The primary endpoint was defined as the difference between the two treatment arms in the peak level of serum aspartate transaminase (AST) within seven days after transplant.

- Following organ retrieval, a markedly different discard rate between the two trial arms resulted in 100 static cold storage (SCS) and 120 NMP livers were available for primary outcome reporting, with 101 SCS and 121 NMP livers available for secondary outcome analysis. This discrepancy in group size reduced the study power to 89.7%.
- The authors reported peak AST during the first 7 days after transplant was reduced by 49.4% in the NMP group compared to static cold storage (SCS) when adjusted by center and donor type ($P < 0.001$). Data to assess early allograft dysfunction (EAD) rates were available in 216 recipients: the odds of developing EAD in the NMP arm (12 out of 119) were 74% lower than the SCS arm (29 out of 97; $P < 0.001$). There was no significant difference in bile duct complications, graft survival or survival of the patient (Nasralla, et al., 2018).

A multicenter randomized controlled trial DHOPE-DCD (Dual Hypothermic Oxygenated Perfusion of DCD Liver Grafts in Preventing Nonanastomotic Biliary Strictures after Transplantation) was conducted. The Liver Assist device (Organ Assist from XVIVO) was used.

- Patients 18 years of age or older who were undergoing liver-only transplantation with a graft from a donor after circulatory death (in controlled circumstances) were eligible for inclusion. Patients were excluded if the body weight of the donor was less than 40 kg or if the donor was positive for the human immunodeficiency virus or hepatitis B or C virus. Patients were also excluded if they were undergoing transplantation for fulminant liver failure or for primary nonfunction after a previous transplantation, were incapable of providing informed consent, were positive for the human immunodeficiency virus, or had a contraindication to undergoing magnetic resonance cholangiography. The donor liver had been deemed to be suitable and had been accepted by the transplantation surgeon for a recipient after circulatory death.
- The primary end point was the incidence of symptomatic nonanastomotic biliary strictures at 6 months after transplantation.
- The reporting study population included 78 patients in the machine-perfusion group and 78 patients in the control group (received a liver after static cold storage only).
- The authors reported nonanastomotic biliary strictures occurred in 6% of the patients in the machine-perfusion group and in 18% of those in the control group ($P = 0.03$).There were no relevant differences between the two groups in the use of renal-replacement therapy, in the durations of stay in the intensive care unit or hospital, or in graft and patient survival at 1 year (van Rijn, et al., 2021).

An open-label, randomized trial was conducted in Italy. The Vitasmart (Bridge to Life) machine was used.

- A total of 110 patients underwent extended criteria donors (ECD) grafts. Donors were considered eligible for the trial if they met the United Network for Organ Sharing (UNOS) criteria for ECD. Exclusion criteria included donor age < 18 years, split-liver recipients, LT for acute liver failure, and the development of intraoperative surgical complications before the organ implantation. Donors after circulatory death (DCD) were also excluded due to the Italian law.
- Patients were randomized to receive a liver after Hypothermic Oxygenated Perfusion (HOPE) or after static cold storage (SCS) alone.
- Median follow-up period was 473 days (15.76 mo). Early allograft dysfunction occurred in seven of the 55 patients (13%) in the HOPE group and in 19 of the 55 patients (35%) in the SCS group ($p = .007$). Post hoc power analysis was performed which showed the study to be slightly underpowered (110 patients enrolled versus a total of 118 required to achieve 80% power) (Ravaioli, et al., 2022).

Czigany et al. (2021) conducted a multicenter RCT assessing peak serum alanine aminotransferase (ALT) during the first seven days following LT as the primary endpoint. End-ischemic HOPE (Liver Assist; Organ Assist) was applied through the portal vein for a minimum of 1 hour before implantation.

- Secondary endpoints included incidence of postoperative complications [Clavien-Dindo classification (CD), Comprehensive Complication Index (CCI)], length of intensive care- (ICU) and hospital-stay, and incidence of early allograft dysfunction (EAD).
- A total of 46 patients undergoing extended criteria donation (ECD) liver transplantation (LT) from donation after brain death (DBD) were included. Half were randomized to hypothermic oxygenated machine perfusion (HOPE) (N=23) and half to static cold storage (N=23).

- All 46 patients were included in the final analysis. The authors concluded that end-ischemic treatment with HOPE led to a significant decrease in the primary endpoint, serum peak ALT, indicating a reduced allograft injury after reperfusion. HOPE resulted in a 47% decrease in serum peak ALT [P=0.030]. The authors noted that lower peak levels of ALT after HOPE also correlate with superior post-transplant outcomes; there was a significant reduction in 90-day complications [P=0.036]. The rate of major postoperative complications (CD grade ≥3) after LT was 44% in HOPE treated allografts versus 74% in the SCS arm.

Mugaanyi et al. (2022) conducted a meta-analysis. The PubMed, Web of Science and Scopus databases were queried for studies reporting on normothermic and hypothermic machine perfusion in liver transplantation through September 2022.

- A total of 10 studies with 1104 liver transplant recipients were analyzed (504 machine-perfused livers and 600 static cold-storage livers). Of the 504 perfused livers, 371 were NMP and 133 were HOPE. In one study, HOPE was combined with normothermic regional perfusion (NRP).
- The authors reported that machine perfusion is associated with more favorable postoperative outcomes. However, there appears to be some difference in the postoperative outcomes of HOPE/D-HOPE vs. SCS and those of NMP vs. SCS. In a pooled analysis of machine perfusion (NMP and HOPE/D HOPE) vs. SCS, graft survival was significantly better in the machine perfusion group. However, the studie**s** were significantly heterogeneous.
- HOPE had a significantly lower incidence of biliary complications than SCS. However, the difference was not significant for NPM vs. SCS, and yet again, the studies were heterogeneous. The authors concluded that HOPE/D-HOPE and NMP are promising alternatives to SCS for donor liver preservation.

Mechanical Perfusion Systems - **Professional Societies/Organizations**

American College of Physicians (ACP): The ACP published a Statement of Concern titled Ethics, Determination of Death, and Organ Transplantation in Normothermic Regional Perfusion (NRP) with Controlled Donation after Circulatory Death (cDCD). It includes but is not limited to the following:

Conclusion and Recommendation
It is tragic when a patient dies awaiting a needed organ. But organ procurement and transplantation must satisfy ethical standards in meeting this need. NRP-cDCD raises profound ethical questions regarding the dead donor rule, fundamental ethical obligations of respect, beneficence, and justice, and the categorical imperative to never use one individual merely as a means to serve the ends of another, no matter how noble or good those ends may be.
The questions and concerns raised here have not been adequately considered to date. Further professional and public discussion of NRP-cDCD-- a protocol more accurately described as organ retrieval after cardiopulmonary arrest and the induction of brain death— is needed. ACP recommends the use of NRP-cDCD be paused. The burden of proof regarding the ethical and legal propriety of this practice has not been met. Sound ethical arguments, not just assertions, must underpin organ procurement methods and such efforts must be consistent with US legal and ethical standards for determination of death. Without this, we risk decreasing public confidence in health care and undermining support for organ donation, further exacerbating the problem this protocol seeks to address.

American Society of Transplant Surgeons (ASTS): The ASTS published Recommendations on best practices in donation after circulatory death organ procurement (ASTS/Croome, et al., 2022):

The Recommendations aim to provide guidance on contemporary issues surrounding donation after circulatory death (DCD) organ procurement in the United States. A work group was composed of members of the American Society of Transplant Surgeon Scientific Studies Committee and the Thoracic Organ Transplantation Committee. The following topics were identified by the group either as controversial or lacking standardization: pre-withdrawal preparation, definition of donor warm ischemia time, DCD surgical technique, combined thoracic and abdominal procurements, and normothermic regional perfusion. The proposed recommendations were classified on the basis of the grade of available evidence and the strength of the recommendation. This information should

be valuable for transplant programs as well as for organ procurement organizations and donor hospitals as they develop robust DCD donor procurement protocols.

Summary of The American Society of Transplant Surgeons recommendations on best practice in donation after circulatory death organ procurement, specific to 'The use of NRP in the United States':

The use of NRP in the United States	Grade of evidence	Strength of recommendation
In many countries, normothermic regional perfusion (NRP) is considered an acceptable practice available to procure organs from DCD donors. When discussing NRP, it is important to specify if the procurement procedure being utilized involves abdominal normothermic regional perfusion (A-NRP) or thoracoabdominal normothermic regional perfusion (TA-NRP).	II-2 (Cohort or case-control analytic studies)	Strong (Strong, factors influencing the strength of recommendation included the quality of evidence, presumed patient-important outcomes, and costs.)
Terminology such as "reanimation," "resuscitation," and "extracorporeal membrane oxygenation" (ECMO) should be avoided when discussing NRP as these terms do not clearly reflect the process of organ recovery from a donor who has already been declared deceased due to hemodynamic arrest. In lieu, more specific and less emotionally laden terms such as "in situ tissue perfusion" or "dynamic in situ organ assessment" should be used.	Expert Opinion III (Opinions of respected authorities, descriptive epidemiology)	Strong
Postmortem A-NRP and TA-NRP are safe and feasible in DCD organ procurement and may increase the organ utilization rate.	II-2	Weak (Variability in preferences and values or more uncertainty. The recommendation is made with less certainty, higher costs, or resource consumption)
The ASTS is supportive of exploring all options to increase organ donations. The ASTS strongly recommends that future guidelines for NRP protocols be developed, including ethical principles, viability assessment, acceptance criteria, and standardization of protocols (ASTS/Croome, et al., 2022).	Expert Opinion III	Strong

American Society of Transplant Surgeons (ASTS): The ASTS published a Statement on Thoracoabdominal Normothermic Regional Perfusion Donation after Circulatory Determination of Death. It was drafted by the ASTS Ethics Advisory Committee, and approved by the ASTS Executive Committee on August 23, 2022. It includes but is not limited to the following:

Definition of the problem
Thoracoabdominal normothermic regional perfusion for donation after circulatory determination of death (TA-NRP DCD) utilizes oxygenated machine perfusion for the preservation of abdominal and thoracic organs rather than standard cold perfusion. After the donor has been pronounced and confirmed dead, and after waiting 2 to 5 minutes after the determination of circulatory death to ensure the decedent does not spontaneously resuscitate, the TA-NRP DCD procedure involves opening the chest, central cannulation, clamping of the brachiocephalic vessels and initiation of normothermic oxygenated perfusion to the organs that will be used for transplantation. The procurement proceeds in the same fashion as a brain-dead donor.

ASTS principles regarding the ethical acceptability of NRP-DCD procurement procedures

- The ethical acceptability of DCD donation is based on 3 fundamental principles: respect for autonomy, nonmaleficence and beneficence.
- Respect for autonomy requires that authorization is obtained for DCD donation as well as for any procedures done or medications administered for organ evaluation or preservation. In addition, the discussion about organ donation in the setting of DCD donation must occur after the decision to withdraw life-sustaining treatments has been made. Further, as is always the case, medical professionals attending to the patient and working with the family through end-of-life care and decisions must be separate and apart from those medical professionals who are part of the organ recovery or transplant team and process.
- Nonmaleficence requires that harm to the donor is avoided. First and foremost, this requires that potential DCD donors are provided with the same level of comfort care measures as individuals who undergo withdrawal of life-sustaining treatments without consideration for organ donation. Second, it requires that the organ procurement procedure commences after the donor is dead so that the procedure itself does not cause death (i.e., the dead donor rule).
- Death in DCD donation is determined by circulatory and respiratory criteria consistent with the legal definition of death in the Uniform Determination of Death Act, which has been adopted in all material respects by almost all states in the US. The UDDA states: “An individual who has sustained either (1) irreversible cessation of circulatory and respiratory functions, or (2) irreversible cessation of all functions of the entire brain, including the brain stem, is dead”. DCD donors are declared dead in accordance with the UDDA and following accepted medical standards by a medical provider who is not a part of the organ procurement team and using the hospital’s criteria for cardio-pulmonary death.
    - After the cessation of circulatory and respiratory function, a hands-off period is observed for irreversibility of circulatory death, during which there is an absence of auto-resuscitation and death is confirmed at the end of that period.
    - Circulatory death *occurs* when the heart and lungs have lost their ability to function within the organism and cannot contribute to the operation of the organism as a whole. Circulatory death is *confirmed* in a DCD donor after a hands-off period in which autoresuscitation does not occur. At that point, the donor is dead and the procurement team is allowed to proceed with organ procurement.
    - Ensuring that the donor is dead is essential to DCD donation because the procurement procedure occurs directly following confirmation of death.
- Beneficence requires that risks are minimized and benefits are maximized in medical procedures. Because DCD donors are dead at the time of donation, they do not benefit from the procedure, but there is benefit to family members who hope that their loved one can help as many others as possible through organ donation. Moreover, increasing the likelihood of benefit to organ transplant recipients is an element of beneficence considering the donor-recipient dyad.
- The ethical acceptability of TA-NRP DCD has been questioned because (1) the heart is re-perfused in the body, which some allege brings into question irreversibly, and (2) the brachiocephalic vessels are clamped before the initiation of NRP, which prevents reestablishment of flow to the brain but which some allege is a contributing cause to the death itself.
- The ASTS supports the ethical acceptability of TA-NRP DCD because this procedure meets the ethical baseline for DCD organ donation as follows: following a family’s decision to cease all life-sustaining therapies for their loved one, authorization is obtained for TA-NRP donation as well as consent for ante-mortem interventions and medications in the same way as it is done for a standard DCD donor; nonmaleficence is fulfilled because the NRP procurement procedure does not start until the donor has been confirmed dead. Our analysis of the specific ethical concerns about TA-NRP DCD are as follows:
    - Perfusion of the organs in the body: This is not autoresuscitation or resuscitation of the donor. The donor is dead before the initiation of NRP. NRP is mechanically assisted regional perfusion and oxygenation of organs for transplantation.
    - Clamping the brachiocephalic vessels before the initiation of TA-NRP ensures that the brain is not reperfused. Circulatory death has already been determined under the UDDA and in accordance with accepted medical standards when the brachiocephalic vessels are clamped.
    - Reperfusing the heart in the body on NRP is no different that restarting the heart outside of the body with machine perfusion. While this is optically different, in both cases, the heart is restarted with artificial machine assistance for the purpose of organ donation in a person who died

intending to donate their organs. The heart would not continue to function within the donor without ventilatory support so it is functioning only with mechanical assistance for the purposes of organ donation.

The ASTS hopes to engage the medical and lay community in open, transparent dialogue about TA-NRP DCD donation to maintain trust in organ donation and demonstrate our commitment to the organ donors who make transplantation possible and save the lives of our patients.

Use Outside of the US
National Institute for Clinical Excellence (NICE**):** A NICE guidance on Living-donor liver transplantation (November 2015) notes that "Current evidence on the efficacy and safety of living-donor liver transplantation appears adequate to support the use of this procedure for suitable donors and recipients with normal arrangements for clinical governance, consent and audit, provided that the necessary regulatory requirements are followed".

Medicare Coverage Determinations

	Contractor	Determination Name/Number	Revision Effective Date
NCD	National	Adult Liver Transplantation (260.1) Pediatric Liver Transplantation (260.2)	9/04/2012 9/01/1991
LCD		No Determination found	

Note: Please review the current Medicare Policy for the most up-to-date information.
(NCD = National Coverage Determination; LCD = Local Coverage Determination)

Coding Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	Description
47133	Donor hepatectomy (including cold preservation), from cadaver donor
47135	Liver allotransplantation, orthotopic, partial or whole, from cadaver or living donor, any age
47140	Donor hepatectomy (including cold preservation), from living donor; left lateral segment only (segments II and III)
47141	Donor hepatectomy (including cold preservation), from living donor; total left lobectomy (segments II, III and IV)
47142	Donor hepatectomy (including cold preservation), from living donor; total right lobectomy (segments V, VI, VII and VIII)
47143	Backbench standard preparation of cadaver donor whole liver graft prior to allotransplantation, including cholecystectomy, if necessary, and dissection and removal of surrounding soft tissues to prepare the vena cava, portal vein, hepatic artery, and common bile duct for implantation; without trisegment or lobe split
47144	Backbench standard preparation of cadaver donor whole liver graft prior to allotransplantation, including cholecystectomy, if necessary, and dissection and removal of surrounding soft tissues to prepare the vena cava, portal vein, hepatic artery, and common bile duct for implantation; with trisegment split of whole liver graft into 2 partial liver grafts (ie, left lateral segment [segments II and III] and right trisegment [segments I and IV through VIII])
47145	Backbench standard preparation of cadaver donor whole liver graft prior to allotransplantation, including cholecystectomy, if necessary, and dissection and removal of surrounding soft tissues

CPT®* Codes	Description
	to prepare the vena cava, portal vein, hepatic artery, and common bile duct for implantation; with lobe split of whole liver graft into 2 partial liver grafts (ie, left lobe [segments II, III, and IV] and right lobe [segments I and V through VIII])
47146	Backbench reconstruction of cadaver or living donor liver graft prior to allotransplantation; venous anastomosis, each
47147	Backbench reconstruction of cadaver or living donor liver graft prior to allotransplantation; arterial anastomosis, each

HCPCS Codes	Description
S2152	Solid organ(s), complete or segmental, single organ or combination of organs; deceased or living donor(s), procurement, transplantation, and related complications; including: drugs; supplies; hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services, and the number of days of pre- and post-transplant care in the global definition

Considered Experimental/Investigational/Unproven when used to report a mechanical perfusion system for use with liver transplantation:

HCPCS Codes	Description
E1399	Durable medical equipment, miscellaneous

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